Lysophosphatidic acid mediates fibrosis in injured joints by regulating collagen type I biosynthesis.

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Public Summary:
This work identifies novel mechanisms mediating healing of articular cartilage tissue after injury. It also identifies novel therapeutic candidates for potential therapy of post-traumatic osteoarthritis.

Scientific Abstract:
OBJECTIVE: Articular cartilage is a highly specialized tissue which forms the surfaces in synovial joints. Full-thickness cartilage defects caused by trauma or microfracture surgery heal via the formation of fibrotic tissue characterized by a high content of collagen I (COL I) and subsequent poor mechanical properties. The goal of this study is to investigate the molecular mechanisms underlying fibrosis after joint injury. DESIGN: Rat knee joint models were used to mimic cartilage defects after acute injury. Immunohistochemistry was performed to detect proteins related to fibrosis. Human fetal chondrocytes and bone marrow stromal cells (BMSCs) were used to study the influence of the lipid lysophosphatidic acid (LPA) on COL I synthesis. Quantitative PCR, ELISA and immunohistochemistry were performed to evaluate the production of COL I. Chemical inhibitors were used to block LPA signaling both in vitro and in vivo. RESULTS: After full-thickness cartilage injury in rat knee joints, stromal cells migrating to the injury expressed high levels of the LPA-producing enzyme autotaxin (ATX); intact articular cartilage in rat and humans expressed negligible levels of ATX despite expressing the LPA receptors LPAR1 and LPAR2. LPA-induced increases in COL I production by chondrocytes and BMSCs were mediated by the MAP kinase and PI3 Kinase signaling pathways. Inhibition of the ATX/LPA axis significantly reduced COL I-enriched fibrocartilage synthesis in full-thickness cartilage defects in rats in favor of the collagen II-enriched normal state. CONCLUSION: Taken together, these results identify an attractive target for intervention in reducing the progression of post-traumatic fibrosis and osteoarthritis.